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Steven B. Kelber
Berenato & White, LLC
6550 Rock Spring Drive
Suite 240
Bethesda, MD 20817

EXAMINER	
HUMPHREY, LOUISE WANG ZHIYING	
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BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Application Number: 10/666,997
Filing Date: September 18, 2003
Appellant(s): CARTER ET AL.

Steven Kelber
For Appellant

EXAMINER'S ANSWER

This is in response to the appeal brief filed 19 November 2009 appealing from the Office action mailed 11 May 2009.

(1) Real Party in Interest

A statement identifying by name the real party in interest is contained in the brief.

(2) Related Appeals and Interferences

The examiner is not aware of any related appeals, interferences, or judicial proceedings which will directly affect or be directly affected by or have a bearing on the Board's decision in the pending appeal.

(3) Status of Claims

The statement of the status of claims contained in the brief is correct.

(4) Status of Amendments After Final

No amendment after final has been filed.

(5) Summary of Claimed Subject Matter

The summary of claimed subject matter contained in the brief is correct.

(6) Grounds of Rejection to be Reviewed on Appeal

The appellant's statement of the grounds of rejection to be reviewed on appeal is correct.

(7) Claims Appendix

The copy of the appealed claims contained in the Appendix to the brief is correct.

(8) Evidence Relied Upon

Yin et al. "Overcoming HIV drug resistance through rational drug design based on molecular, biochemical, and structural profiles of H IV resistance." Cellular and Molecular Life Sciences, Vol. 63, No. 15 (August 2006), p. 1706-1724.

Hendrix et al. "Pharmacokinetics and Safety of AMD-3100, a Novel Antagonist of the CXCR-4 Chemokine Receptor, in Human Volunteers." ANTIMICROBIAL AGENTS AND CHEMOTHERAPY, Vol. 44, No. 6 (June 2000), p. 1667-1673.

Gait et al. "Progress in anti-HIV structure-based drug design." Trends in Biotechnology, Vol. 13, No. 10 (October 1995), p. 430-438.

(9) Grounds of Rejection

The following ground of rejection is applicable to the appealed claims:

Claims 93, 94 and 132-134 are rejected under 35 U.S.C. §112, first paragraph, as failing to comply with the enablement requirement. The claims contain subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

In making a determination as to whether an application has met the requirements for enablement under 35 U.S.C. 112, first paragraph, the courts have put forth a series of factors. See, In re Wands, 8 USPQ2d 1400, at 1404 (CAFC 1988); and Ex Parte Forman, 230 U.S.P.Q. 546 (BPAI 1986). The factors that may be considered include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims. Id. While it

is not essential that every factor be examined in detail, those factors deemed most relevant should be considered.

Claims 93, 94 and 132-134 are directed to a method of inhibiting human immunodeficiency virus (HIV) particle generation in cells comprising administering a peptide comprising a PTAP motif that inhibits binding between tumor susceptibility gene (Tsgl01) protein and HIV Gag polypeptide.

The breadth of the claims encompasses inhibiting HIV particle formation in any kinds of cells, including *in vivo* and *in vitro*, suspected to be infected by any strain or subtype of HIV by inhibiting the binding of any form of Tsg101 and the Gag protein of any strain or quasi-species of HIV. With the exception of claim 132 limiting the peptide to comprise SEQ ID NO:4, the claimed peptide is a genus of variants with different length from the four amino acid peptide, PTAP, to any size large protein containing the four amino acids, PTAP. Further, claims 93, 94 and 132 do not claim whether the anti-HIV peptide acts on a target that is conserved among all hosts.

The disclosure does not provide any working embodiments that meet the claimed limitations. While there is one cell culture example (page 37- 41) identifying the binding regions of Gag p6 late domain and Tsg101 and mutating by deletion of the binding region in either Tsg101 or Gag protein to observe the effect on particle release by HIV vector-transfected COS cells, there is no *in vitro* or *in vivo* working example that shows the effectiveness of any PTAP-containing peptides in inhibiting particle formation. Furthermore, the Gag p6 late domain does not represent the entire genus of the PTAP-

containing peptides. The Gag protein is neither conserved between the two HIV serotypes, HIV-1 and HIV-2, nor among the abundant strains or quasi-species of HIV. Therefore, the peptide binding affinity/avidity is questionable.

The specification provides no guidance regarding practice of the claimed method. The amount of direction is limited to one cell culture assay identifying the binding regions in HIV Gag p6 late domain and Tsg101 (Example 1) and the amount of released mature HIV particles as a result of mutated binding regions in Tsg101 and HIV Gag p6 late domain (Example 2). The disclosed example is not even a test of a peptide inhibitor for the interaction between Tsg101 and Gag. There is no evidence that shows any correlation with *in vitro* or *in vivo* peptide inhibition efficacy to confirm the Applicant's theory deduced from the cell culture results. There is no teaching about the inhibition properties such as the binding specificity, selectivity and affinity, neither is there any teaching about the therapeutic properties such as oral bioavailability, cellular uptake, toxicity, lethal dose, and side effects for administering a PTAP-containing peptide into a cell inside a body. There is not even a test to determine the efficacy and resistance of the claimed genus of Tsg101 binding inhibitors. Therefore, the disclosure does not relate to inhibiting HIV particle formation in cells *in vitro* or *in vivo*.

There is a high level of uncertainty and unpredictability in the art. The development of suitable HIV-1 inhibitors has been an arduous and empirical process, often ending in failure (Hendrix, 2000, first and last paragraph; Gait, 1995). This is due to a number of factors: (1) failure to understand the molecular determinants modulating many viral protein and host cell factor interactions; (2) failure of *in vitro* tissue culture

studies and *in vivo* animal models to adequately predict clinical efficacy; (3) failure of many compounds to have acceptable pharmacological profiles despite initial favorable *in vitro* and *in vivo* activities; and (4) failure of related structural analogs to function in the desired manner, which provides further evidence of the specificity of these molecular interactions. The challenges of developing efficacious anti-HIV agents are best summarized by Gait and Karn (1995) who state in the Conclusions (p.37): There can be few tasks in biotechnology that are more challenging than designing antiviral drugs. All of the protease inhibitors that have entered into clinical trials are potent inhibitors of HIV-1 replication in cell culture, and exhibit remarkable selectivity for the viral enzyme. Unfortunately, early protease inhibitors tended to suffer from problems of short serum half-life, poor availability and rapid clearance. As these pharmacokinetic problems have been addressed and solved, new difficulties have emerged from the resultant clinical experience, such as sequestration of the drug by serum proteins, drug resistance and uneven distribution throughout the body. Since these types of problems are unpredictable, it remains necessary to take into account the pharmacological parameters in any drug development program at the earliest possible stage.

The art of HIV particle inhibitors is highly unpredictable because the effect of such a compound appears to change due to pharmacokinetic variation, fluctuating adherence, the emergence of drug resistant mutations and/or other factors. Inadequate drug concentrations can result from a number of factors including non-adherence, pharmacokinetics, and lack of drug potency. In addition, anatomical sanctuary sites may exist, either *in vitro* or *in vivo*, where drug concentrations do not achieve adequate

levels despite apparent therapeutic serum drug concentrations. HIV replication can occur in such settings, and the selective pressure of antiretroviral therapy leads to the emergence of HIV harboring drug-resistant mutations. Thus, a key element in future drug design strategies is to understand how drug resistance mutations affect the interaction of the drug with its target, and to then develop compounds with the adaptability to inhibit these variants along with wild-type HIV (Yin, 2006). Therefore, efforts to develop effective treatments must overcome the complex evolutionary dynamics in HIV-infected individuals and within affected populations.

In the instant case, a Tsg101-Gag binding inhibitor as an AIDS drug is not considered routine in the art. The disclosure fails to address any of the aforementioned caveats in the development of an antiviral agent. Without sufficient guidance to the safety, bioavailability, plasma concentration, and antiviral effect, the experimentation left to those skilled in the art is undue or unreasonable under the circumstances.

For the reasons discussed above, it would require undue and unpredictable experimentation for one skilled in the art to use the claimed method.

(10) Response to Argument

Appellant has presented the following arguments: (1) Claims 132 and 134, which recite a specific peptide for administration, may be independently patentable (page 10 of the Appeal Brief); (2) the claimed invention is not therapy or treatment for HIV infection because it makes no difference if the cell to which the peptide is administered is a cell of a human being, and if it is, if that human being suffers from AIDS or not, and

if it does, if the AIDS sufferer dies, survives or improves (page 10-13); (3) The very long specification demonstrates by specific examples, including assays and results, that peptides of the type recited do indeed inhibit binding between Tsg101 protein and Gag polypeptide; and (4) Issuance of U.S. Patent 7,494,767 supports enablement of the claimed invention.

Appellant's arguments are found unpersuasive. In response to Appellant's allegation about the patentability of claims 132 and 134, it is respectfully submitted that Appellant does not provide any reason or evidence that demonstrates the claimed SEQ ID NO:4 indeed inhibits binding between Tsg101 protein and HIV Gag polypeptide. The specification only discloses that SEQ ID NO:4 binds both Tsg101 and HIV Gag but does not describe any inhibition of Tsg101 and HIV Gag binding and thereby inhibition of HIV particle generation as a result of SEQ ID NO:4 binding. The fact that SEQ ID NO:4 can bind both Tsg101 and HIV Gag does not rule out the possibility that SEQ ID NO:4 can form a complex with Tsg101 and HIV Gag and thus bring the two proteins together. Appellants cannot equate the observation of SEQ ID NO:4 binding both Tsg101 and HIV Gag with the desired result of inhibiting binding between Tsg101 and HIV Gag without any supporting evidence and/or scientific reasoning.

In response to Appellant's contention that the claimed invention is not treatment or therapy of HIV, it is respectfully submitted that the rejected claims are directed to administering a PTAP peptide to cells suspected of being infected with HIV, which encompass both culture dish cells and human body cells. The latter reads on administering a PTAP peptide to a living host cell, which would be a cell inside a human

since humans are the natural hosts of HIV infection. Appellant's own interpretation of the claimed invention seems to be out of alignment with the claim limitations. The claims do not limit "the cell" to be the *in vitro* cells. Therefore, the claim limitation "administering to cells" reads on administering to cells in a human as well as to cells in a culture dish and "inhibition of particle formation" reads on both *in vitro* and *in vivo* HIV particle inhibition. Appellants' assertion that inhibition of particle formation is distinct from treating HIV infection is not based on any grounds. A method of inhibiting HIV infection of cells via inhibiting particle generation in a cell is known to one of ordinary skill in the art as *in vitro* and *in vivo* treatment of HIV infection because inhibition of particle generation is a mechanism of treatment. Nevertheless, Appellants concede that "in Applicant's invention, the infected cell is not saved, is not treated" (see page 12), which seems to admit that the claimed method of inhibiting HIV infection, and specifically, inhibiting HIV particle generation is not enabled by the description as filed.

Examiner respectfully disagrees with Appellant's allegation that the specification demonstrates that the recited peptides do indeed inhibit binding between Tsg101 protein and Gag polypeptide. The described method of identifying HIV Gag binding region peptides is a long way from the claimed method of inhibiting HIV particle generation in cells. The instant application merely discloses the identification of the binding region between HIV Gag and Tsg101 and effect of mutation in the Gag late domain on particle release *in vitro*, which cannot be extrapolated to a method of identifying peptides blocking the PTAP region of Gag protein from interacting with Tsg101, which is not even representative or predictive of the effectiveness of any

PTAP-containing peptides inhibiting HIV particle formation in any cells, especially cells inside a human body. Applicants have not provided any evidence that validates the theory that a PTAP-containing peptide of any length is an effective inhibitor of Gag-Tsg101 binding and reduces particle formation. The disclosed example is not even a test of a peptide inhibitor for the binding between Tsgl01 and Gag. There is no evidence that shows any correlation with *in vitro* or *in vivo* particle inhibition to confirm the Applicant's theory deduced from identifying the late domain in HIV Gag as the binding region for Tsg101 protein and from observing particle formation as a result of Tsg101 binding Gag. There is no teaching about the inhibition properties such as the binding specificity, selectivity and affinity, and the pharmacokinetic properties such as oral bioavailability, cellular uptake, toxicity, lethal dose, and side effects for administering a PTAP-containing peptide into a cell inside a body. There is not even an *in vitro* test to determine the efficacy and resistance of the claimed genus of Tsg101-Gag binding inhibitors in any cells. In short, the specification never discloses any PTAP peptide that effectively inhibits Gag-Tsg101 binding and inhibits HIV particle generation. The sentences in paragraph [0012] teaching a method of identifying a peptide inhibitor does not disclose the actual peptide as claimed that is capable of inhibiting Tsg101-Gag binding and inhibiting HIV particle generation. Therefore, the disclosure is not relevant to the claimed method of inhibiting HIV particle formation in cells *in vitro* or *in vivo* and raises the issue of unpredictability and undue experimentation when considering the enablement of the disclosure as filed.

In response to Appellant's contention that the Examiner's issuance of the parent case to the U.S. patent 7,494,767 demonstrates that the Office has conceded that what is claimed is enabled. This is certainly not the Examiner's position. First of all, Appellant is reminded that patents are issued based on the claims not the specification and that every case is evaluated on its own merits. Applicants' argument regarding the identical specification in the U.S. Patent 7,494,767 is not germane to the rejection at issue. Second, it is respectfully pointed out that the two sets of claims in the parent case and in the current application are directed to entirely different methods. The fact pattern of the instant application is different from that of the U.S. Patent 7,494,767. Appellant does not seem to grasp the fundamental difference between the described method of identifying peptide inhibitors and the claimed method of inhibiting HIV particle generation comprising administering peptides comprising a PTAP motif that inhibits binding between Tsg101 protein and HIV Gag polypeptide. As already set forth in all previous Office Actions and reiterated above, a method of identifying inhibitors for the binding of HIV Gag and Tsg101 does not disclose any actual effective peptide inhibitors that can be administered in a method of inhibiting HIV particle generation in cells. Therefore, the claimed invention differs from the patented invention.

In summary, Examiner's rejection is based on the following issues: (1) the lack of any demonstration of particle inhibition activity of any PTAP-containing peptide, neither *in vitro* nor *in vivo*; (2) the high level of unpredictability in the *in vitro-in vivo* correlation for HIV inhibition; (3) the heterogeneity of the HIV affecting the inhibitor binding affinity and efficacy. Applicants have not addressed any of these issues in their responses.

Applicants have not responded to the fact that the claim limitation "cells" reads on both cell culture and living cells in a human body, which means HIV inhibition treatment/therapy, hence Examiner presented the issues of satisfying the therapeutic properties for administering a PTAP-containing peptide into a cell inside a body, as well as the challenges for the development of a HIV inhibitor that are well known to one skilled in the art. Therefore, the rejection of record is considered to be proper.

(11) Related Proceeding(s) Appendix

No decision rendered by a court or the Board is identified by the examiner in the Related Appeals and Interferences section of this examiner's answer.

For the above reasons, it is believed that the rejections should be sustained.

Respectfully submitted,

/L. H./

Examiner, Art Unit 1648

Conferees: (SPE Nickol and Mondesi)

/Gary B. Nickol /

Supervisory Patent Examiner, Art Unit 1646

/Robert B Mondesi/

Supervisory Patent Examiner, Art Unit 1645